



NOTES

RICKETTSIAL DISEASES

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Vector-borne obligate intracellular bacteria; poor Gram staining, rod-shaped structure
- Common tropism for endothelial cells → variable amount of hemorrhage, edema, organ dysfunction

SIGNS & SYMPTOMS

- Disease-specific; fairly consistent integument manifestations (e.g. rash)

DIAGNOSIS

LAB RESULTS

- Isolation of *Rickettsiae*
 - Inoculation of animal/via cell culture
- Serology
 - Enzyme-linked immunosorbent assay (ELISA), western blot, microimmunofluorescent antibody test (detection of bacterial-specific antigens)

- Immunologic detection in tissue
 - Isolation in epithelial tissue (from integument involvement)
 - Requires sophisticated laboratory capability (not common in endemic areas of disease)
- Polymerase chain reaction (PCR)
 - Detection of rickettsial DNA

OTHER DIAGNOSTICS

- Clinical presentation (disease-specific)

TREATMENT

MEDICATIONS

- Prompt antimicrobial therapy
 - Doxycycline (preferred)

VISIT...

LANZAROTE
Caliente.COM

ANAPLASMA

osms.it/anaplasma

PATHOLOGY & CAUSES

- Tick-borne, obligate intracellular bacteria, endemic to wooded areas in North America → self-resolving disease, AKA human granulocytic anaplasmosis (HGA)

Vector

- *Anaplasma phagocytophilum*: *Ixodes* tick
 - *Ixodes scapularis*: also transmits *Borrelia burgdorferi*, *Babesia* spp. in eastern United States (US)
 - *Ixodes pacificus*: main vector in western US
 - *Ixodes ricinus*: implicated in European disease

Life cycle and transmission

- Reservoir hosts: deer, white-footed mice (source of disease, not affected by pathogen)
- Vector: *Ixodes* tick (connects organism from reservoir to target)
- Human transmission

Pathogenesis

- Tick bite → blood circulation → leukocyte infection, membrane attachment → phagocytosis → replication (in early endosome of leukocyte) → dysfunctional vacuolization, immature lysosomal micelles → microcolony (AKA morulae) development → release into extracellular space after cell lysis/exocytosis
 - P-selectin glycoprotein (identified binding domain for *A. phagocytophilum*)
 - Ligand: P-selectin glycoprotein ligand-1 (PSGL-1) required on granulocytes for internalization

Disease: HGA

- Direct leukocyte cell death
- Inflammatory response → perivascular inflammatory infiltrates in multiple organ systems (without organ failure/endothelial damage)

RISK FACTORS

- Residence in/travel to wooded areas in North America
 - Especially during peak tick activity (e.g. spring, summer)
- Direct contact with slaughtered deer
- Occupational exposure (e.g. military)

COMPLICATIONS

- Co-infection with *Borrelia burgdorferi*, *Babesia* spp.
- Respiratory insufficiency, renal failure, septic shock
- Neurological
 - Demyelinating polyneuropathy, brachial plexopathy
- Serious, fatal opportunistic infections
 - *Herpes simplex* esophagitis, invasive aspergillosis,

SIGNS & SYMPTOMS

- Onset 1–2 weeks after identified tick bite
- Fever, malaise, headache
- Rash
 - Typically trunk (sparing hands, feet), maculopapular (more evident in children)
- Gastrointestinal (GI) symptoms infrequent
- Neurological (rare)
 - Mental status change, meningismus, clonus

DIAGNOSIS

LAB RESULTS

- Leukopenia
 - Specific to disease (neutropenia)
- ↑ hepatic enzymes, lactate dehydrogenase

- **Serology:** indirect IFA
 - Detection of IgG/IgM antibodies of *Anaplasma* species
 - If negative on acute serum testing, repeat with convalescent serum (confirms diagnosis if ↑ fourfold in IgG antibody titer)
- **Whole blood PCR**
 - Detects *epank1* primers on genogroup *A. phagocytophilum*
- **Wright stain:** morulae of *Anaplasma* in leukocyte
 - *A. phagocytophila*: peripheral blood neutrophils; 25–75% (highest among morulae-producing bacteria)

OTHER DIAGNOSTICS

- **History**
 - Tick bite in endemic area

TREATMENT

MEDICATIONS

- Prompt antibacterial management
 - Doxycycline (if pregnant, rifampin); chloramphenicol

OTHER INTERVENTIONS

- **Prevention**
 - Avoid tick habitats
 - Careful inspection after outside activity in wooded areas (esp. in spring, summer); rapid discovery, tick removal < 24–48 hours post bite → effective prophylaxis
 - Skin application of insect repellants
 - Proper clothing for outside work/play (light-colored, long pants tucked into socks, long-sleeved shirts)



Figure 95.1 Mites of the genus *Ixodes* act as vectors for many rickettsial diseases.

COXIELLA BURNETII (Q FEVER)

osms.it/coxiella-burnetii

PATHOLOGY & CAUSES

- *Coxiella burnetii*: primarily zoonotic pathogen → febrile illness (after contact with animal amniotic fluid/placental contents)

Taxonomy

- Order: Legionellales
- Family: Coxiellaceae

Morphology

- Short, pleomorphic rod
 - Strict intracellular bacterium

Life cycle

- Source of human infections
 - Farm animals (e.g. cattle, goats, sheep)
 - Wild animals (e.g. birds, rabbits, reptiles)
 - Arthropods (e.g. ticks)
- Main reservoir
 - Ticks

Transmission

- Inhalation of spores/bacteria
 - Animal feces, milk, products of conception
- Ingestion of contaminated milk
- Percutaneous
 - Crushing of ticks near skin breaks
- Vertical spread (transplacental)

Pathogenesis

- Host cell
 - Macrophage
- Antigenic variation (AKA phase variation) important in virulence
 - Lipopolysaccharide capsule modifications underly antigenic variation

RISK FACTORS

- Occupation involving animal contact (e.g. veterinarian, farmer)
- ↑ age
- Unpasteurized milk consumption

COMPLICATIONS

- Q fever pneumonia, chronic hepatitis, osteomyelitis
- Infective endocarditis
 - Pre-existing heart/valve disease predisposes to endocarditis development
 - May have secondary, septic embolic manifestation

SIGNS & SYMPTOMS

- Q fever (sudden onset)
 - Fever, headache (often frontal), general malaise, cough, anorexia, myalgia
- Pneumonia
 - Cough, pleural effusion
- Hepatitis
 - Hepatomegaly

DIAGNOSIS

LAB RESULTS

- ↑ serum hepatic enzymes, leukopenia/leukocytosis, thrombocytopenia
- Immunofluorescent antibody assays: detect IgM/IgG antibodies; differentiate between acute, chronic infection
 - IgM: detectable 4 days after symptom onset
 - IgG: detectable 9–14 days after symptom onset
 - Concentration of serum samples can assist in diagnosis (esp. if vague clinical presentation)

- PCR
 - Blood/serum detection possible before IgM serology peak
- Immunohistochemistry
- Culture

OTHER DIAGNOSTICS

- History
 - Animal contact, occupation

TREATMENT

MEDICATIONS

- Prompt antimicrobial treatment
 - **Doxycycline**: effectiveness of antibacterial agent, severity of complications warrants use despite side effects; shorter therapy for children (14 day course)

- **Trimethoprim-sulfamethoxazole**: pregnant individuals; treat even if asymptomatic
- **Chronic infection**: prolonged therapy
 - 18 months doxycycline, hydroxychloroquine (monitor serologic response across therapeutic intervention; biannual ophthalmic examinations required)

OTHER INTERVENTIONS

- Management
 - Individuals with pre-existing valvulopathy/cardiomyopathy; echocardiogram
- Prevention
 - Whole cell vaccine; recommended for individuals working with farm animals (e.g. farmers, slaughterhouse workers)

EHRlichia

osms.it/ehrlichia

PATHOLOGY & CAUSES

- Tick-borne, obligate intracellular bacteria with leukocytic tropism, associated with febrile disease with rare, serious neurologic complication
 - AKA human monocytic ehrlichiosis (HME)
- Characteristics
 - Small (0.5–1.5 micrometer) gram-negative cocci, (1.8 megabases) genome

TYPES

- *Ehrlichia ewingii*
 - Southeastern, central United States
- *Ehrlichia chaffeensis*
 - Northeastern, midwestern United States
- *Ehrlichia sennetsu*
 - Western Japan

Vector

- *Amblyomma americanum* (AKA lone star tick)
 - *Ehrlichia ewingii*, *Ehrlichia chaffeensis*

Life cycle

- Tick bite → blood circulation → leukocyte infection, membrane attachment → phagocytosis → replication (in early endosome of leukocyte) → dysfunctional vacuolization, immature lysosomal micelles → microcolony (AKA morulae) development → release into extracellular space after cell lysis/exocytosis

Pathogenesis

- Direct leukocyte cell death
- Inflammatory response → perivascular inflammatory infiltrates in multiple organ system without organ failure/endothelial damage

Disease: Sennetsu fever

RISK FACTORS

- Residence in/travel to western Japan
- Occupational exposure (e.g. military)

COMPLICATIONS

- Co-infection with *Babesia spp./B. burgdorferi*
- Encephalitis, seizure
 - Associated most with *E. chaffeensis*
 - May result in persistent neurologic deficit (rare; seen especially in children)
- Heart failure, respiratory insufficiency, renal failure, shock

SIGNS & SYMPTOMS

- Sennetsu fever
 - Abrupt-onset fever, chills, headache, malaise, sore throat, myalgias, arthralgias
- Atypical rash
 - Maculopapular with occasional petechiae; located on trunk (sparing hands, feet)
- Generalized lymphadenopathy
 - Most associated with *E. sennetsu*; includes hepatosplenomegaly
- GI
 - Associated with *E. chaffeensis*
 - Anorexia, diarrhea, nausea, vomiting

DIAGNOSIS

LAB RESULTS

- Serology: indirect IFA
 - Detection of IgG/IgM antibodies (*Ehrlichia* species)
 - If negative on acute serum testing, repeat with convalescent serum (confirms diagnosis if fourfold increase in IgG antibody titer)
- Whole blood PCR: detects 16S rRNA gene
- Wright stain: morulae (*Ehrlichia*) in leukocyte
 - *E. ewingii*: in peripheral blood granulocyte
 - *E. chaffeensis*: in peripheral blood monocyte

- Leukopenia, thrombocytopenia, anemia, hyponatremia
- Hepatic transaminitis: most common in *E. chaffeensis* infection
- Cerebrospinal fluid (CSF) analysis: pleocytosis (mononuclear cells with morulae), ↑ protein

OTHER DIAGNOSTICS

- History
 - Tick bite in endemic area

TREATMENT

MEDICATIONS

- Prompt antibacterial management: doxycycline, chloramphenicol

OTHER INTERVENTIONS

Prevention

- Avoidance of tick habitats
- Careful inspection after outside activity (esp. in spring, summer)
 - Rapid discovery, removal < 24–48 hours after bite → effective prophylaxis
- Proper skin application of insect repellants

RICKETTSIA RICKETTSII (ROCKY MOUNTAIN SPOTTED FEVER)

osms.it/rickettsia-rickettsii

PATHOLOGY & CAUSES

- Tick-borne, obligate intracellular, Gram-negative bacteria endemic to parts of North America → potentially lethal febrile disease
- Characteristics
 - Weakly gram-negative, nonmotile coccobacillus; 0.7–2.0 micrometers: cannot be visualized by traditional staining methods/direct fluorescent antibody techniques
 - **Bacterial contents:** ribosome; single, circular chromosome; microcapsule surrounding cell wall (may be important in pathogenicity)

Vectors

- *Dermacentor variabilis* (American dog tick)
 - Eastern, South-central US
- *Dermacentor andersoni* (Rocky Mountain wood tick)
 - West of Mississippi River
- *Rhipicephalus sanguineus* (common brown dog tick)
 - Southwestern US
- Virulence of strain depends on tick's feeding status
 - ↑ feeds → ↑ incubation at high temperatures → ↑ extracellular slime → ↑ virulence (AKA reactivation phenomenon)

Life cycle

- Tick bite (requires 6–10 hours of feeding) → proliferates by binary fission
- Grows in nucleus, cytoplasm of host cells

Pathogenesis

- Tropism for endothelial cells, downstream systemic effects as sequelae
- **Endothelial cell entry:** rickettsial outer membrane proteins (rOmps) interact with

lipopolysaccharides, surface-exposed proteins (SEPs) for entry

- rOmps bind Ku70 (membrane protein) → activate Ku70 → recruit ubiquitin ligase → ubiquitination of Ku70 → act upon cAMP receptors protein kinase A, Epac (exchange protein) → rearrangement of host cell actin filaments → rickettsial endocytosis
- **Bacterial spread:** *R. rickettsii* express phospholipase D, tlyC → lyse phagosomal membrane → entry into cytosol → polymerization of host cell monomeric actin filaments → invagination of host cell membranes → passage into neighboring cells
- Further bacterial spread
 - Filopodia (from host cell membranes) assist in intercellular movement
 - Bloodstream, lymphatic spread assist in more distant infection sites
- Small blood vessel injury (not entirely elucidated)
 - Associated with phospholipase A activity, protease activity, free radical-induced lipid peroxidation
 - Cell necrosis (from other infected cells) → CD8⁺ T-cell response → endothelial cell injury → immune, phagocytic cellular response → lymphohistiocytic vasculitis
- **Sequelae of small vessel injury:** ↑ fluid in interstitial space → exposes brain, lung parenchyma to devastating pathophysiologic consequences
- Ability to spread cell-to-cell without causing obvious damage
 - Rarely accumulate in large numbers inside cells
- Speeds of 4.8m/min
 - Achieves speed via rapid recruitment, polymerization of host cell actin filaments

RISK FACTORS

- Residence in/travel to endemic areas (esp. in spring, summer)
- ↑ age (peak: 40–64)
- Individuals who are biologically male
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency

COMPLICATIONS

- Skin necrosis at sites of terminal arterial supply (e.g. fingers, toes, nose, ears, genitals)
- Interstitial pneumonitis, myocarditis, encephalitis

SIGNS & SYMPTOMS

- Early infection
 - Fever, headache, malaise, myalgias, arthralgias, nausea (without vomiting), edema (esp. in children)
- Rash development (hallmark of infection)
 - Blanching, erythematous rash
 - Macules (1–4mm) → petechiae
 - Ankles, wrist → truncal spread → palms, soles rash (characteristic of late-stage disease)
- Confusion, conjunctival erythema, seizures, focal neurologic deficit
- Fundoscopic examination
 - Retinal vein engorgement, arterial occlusion, flame hemorrhage

DIAGNOSIS

DIAGNOSTIC IMAGING

Chest X-ray

- Interstitial infiltrates

Echocardiogram

- Minimal myocardial dysfunction with normal capillary wedge pressure
- Consistent with noncardiogenic nature of pulmonary edema (commonly present)

LAB RESULTS

- Thrombocytopenia (worsens with progression of disease)

- Advanced disease
 - Hyponatremia (sign of central nervous system involvement); transaminitis; ↑ bilirubin; azotemia (due to hypovolemia); ↑ prothrombin, partial thromboplastin times
- CSF
 - Pleocytosis (monocytic, polymorphonuclear predominance possible), ↑ protein

OTHER DIAGNOSTICS

- History
 - Residence in/travel to endemic area; recollection of tick bite (only 30% of individuals recollect bite)

TREATMENT

MEDICATIONS

- Early treatment: prompt, empiric antimicrobial therapy with doxycycline (first-line), chloramphenicol (second-line)
 - Even if mild symptoms (due to potential lethality of bacterial strain); recommended for pregnant individuals, children
 - Goal: initiate < five days after symptom onset
 - Duration: until three days after resolution of febrile illness; minimum seven days
- Antiemetics, antimotility agents (individuals intolerant of doxycycline)

OTHER INTERVENTIONS

- Hemodynamic monitoring in ICU setting; respiratory support; renal replacement therapy, blood transfusions
- Prevention
 - Vigilant detection, early removal of ticks, proper clothing

RICKETTSIA TYPHI (MURINE TYPHUS)

osms.it/rickettsia-typhi

PATHOLOGY & CAUSES

- Rat-borne zoonotic disease **transmitted to humans via flea**; flu-like illness; minority of individuals require ICU-level care
 - AKA murine, endemic, flea-borne typhus

Transmission

- **Zoonotic reservoir:** *Rattus typhi*
- **Vector:** *Xenopsylla cheopis* (AKA Oriental rat flea)

Life cycle

- Flea feeds on infected rodent → lifetime infection → fecal bacterial shedding → human contact with flea feces through breaks in skin barrier/inhalation → human disease
 - Further human infection occurs via body lice passed human-to-human
- Replicates in high titers in yolk sacs of embryonated chicken eggs

Pathogenesis (not well elucidated)

- Perivascular infiltration with lymphocytes, macrophages, plasma, mast cells (on biopsy)
- Vasculitis (rare)
 - Accompanied by mural/intimal thrombi; heart, lungs, kidneys, central nervous system (CNS)
- Disease
 - Mild, flu-like illness

RISK FACTORS

- Warmer climates, seaports, major commercial areas

COMPLICATIONS

- Shock, sepsis, myocarditis, renal/respiratory failure, severe hemolysis (associated with

G6PD deficiency)

- Neurological
 - Meningitis, meningoencephalitis, facial paralysis, hearing loss, ocular abnormalities

SIGNS & SYMPTOMS

- Fever (8–16 days after exposure), chills, headache (commonly frontal), myalgia, **rash** (concurrent with fever; maculopapular, less commonly petechial; **sparing** face, **palms**, **soles**), nausea, vomiting

DIAGNOSIS

LAB RESULTS

- ↑ erythrocyte sedimentation rate (ESR)
- Left shifted leukocyte count (absolute neutropenia/lymphopenia possible)
- Abnormal hepatic enzymes
- Electrolytes
 - Hyponatremia, hypokalemia, ↑ serum creatinine

TREATMENT

MEDICATIONS

- Prompt **doxycycline** antimicrobial therapy
- Ciprofloxacin (viable alternative)

OTHER INTERVENTIONS

Prevention

- Rodent, flea eradication
- Rat-proofing homes, food service areas
- Protective clothing for occupational exposure to rats